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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,623	08/27/2001	Xianxhang Yu	035879-0125	2349

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,623	YU ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-11,13-32,34-50 and 52-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-11, 13-32, 34-50 and 52, 53, 58--60* is/are rejected.

7)☐ Claim(s) *54-57* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/13/04; 2/9/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 13, 14, 22, 34, 35, 40 and 52-54 have been amended. Claims 12, 23 and 51 have been canceled. Claims 1-11, 13-32, 34-50 and 52-60 are pending and under consideration.

The rejection of claims 1-11, 21-32, 40-50, 58-60 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for how to make procytotoxins comprising cytolytic peptides having amphipathic alpha-helical structures and how to use said protoxins in the targeting of cancer cells, does not reasonably provide enablement for how to make procytotoxins which do not comprise amphipathic alpha-helical structures is maintained for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

When given the broadest reasonable interpretation, the "cytotoxin peptides" of the instant invention include any peptide based cytotoxin, such as the vaculating toxin of helicobacter pylori as well as pore-forming cytolytic peptides which exhibit amphipathic alpha-helical structures. In the case of said pore-forming cytolytic peptides having amphipathic alpha helical structures,

there is a nexus between the cytolytic activity of the peptide and the specific three-dimensional structure of the peptide. It would be expected that attachment of peptides and amino acids via epsilon bonds to any of these peptides would inactivate said peptide because the ability to form the pore in a target cell is the result of the three dimensional structure and the property of the modified structure of one type of amphipathic alpha-helical structure would have a nexus with the modified structure of another type of amphipathic alpha-helical structure. However, the broadly based "cytotoxin peptides of the invention doe not have a similar structure so the result of structural modification cannot be predicted by analogy from amphipathic alpha-helical peptides. Thus, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make a procytotoxin comprising for instance, the vacA toxin of H. pylori because one of skill in the art would not know the structural requirements for the amino acid or peptide inactivator of the toxin, nor where to link the inactivator within the structure of the pseudomonas exotoxin molecule.

The specification states that another example of a cytolytic peptide can be found by screening cyclic D,L-alpha peptides for activity against mammalian cells and using said cyclic peptides isolated thereby to form structures wherein the peptide is attached to a peptide matrix metalloproteinase cleavage site which is linked via an epsilon bond to a microbead (paragraph 21). The specification cites Fernandez-Lopez et al (Nature, July 2001, Vol. 412, pp. 452-329) in support of the cyclic peptides. Upon review of said article it is noted that the peptides were optimized for adherence to adherence to bacterial cells. It is noted that one of the peptides (peptide 4) was screened for activity against a melanoma cell line. Fernandez-Lopez et al teach that the MIC against the melanoma cells is greater than 25 times the MIC for S aureus. Thus, in order to carry out the instant invention with cyclic peptides, one of skill in the art would be required to optimize and screen for cyclic peptides that had lytic activity against mammalian cells. Such experimentation is in the realm of undue experimentation because it would precede the actual making of the modified structure.

Further, the art (Ghadiri, WO03092632) teaches that cyclic peptides are believed to self-assemble into supramolecular structures within or by association with cancer cell membranes, wherein said supramolecular structures (nanotubes, barrels of associated, axially parallel nanotubes, a carpet of associated nanotubes) can selectively induce cancer cell membrane

depolarization or disruption while not depolarizing or disrupting normal cell membranes to a substantial or undesired degree. Thus, it can be reasonably concluded that it is the action of the supramolecular structure rather than the single molecule of cyclic peptide which exhibits cytotoxicity. Ghadiri (ibid) also teaches that small changes in amino acid sequence of a cyclic peptide can be amplified into large differences at the supramolecular level. Thus, changes in the structure of a cyclic peptide may constrain peptide interaction and limit formation of supramolecular structures to particular cellular membranes that have particular membrane constituents, membrane partitioning properties, uptake properties, and the like. It can be construed from this teaching that the modification of a cyclic peptide by means of attaching an amino acid or linker peptide via and epsilon bond, or attachment of a microbead, phage or phage filament, all of which are much larger than the single cyclic peptide molecule, would inhibit the formation of the supramolecular structure necessary for membrane selectivity. Further, an additional degree of complexity is added to the system because Ghadiri teaches that the assembly of the supramolecular structures occurs through association with the cancer cell membrane, because the cancer cell membrane in itself is complex and because different cancer cells would have different proteins on the membrane which could react in a different way with the modified cyclic peptide. Given the lack of teachings in the specification regarding the issues above one of skill in the art would be subject to undue experimentation in order to make and use the broadly claimed procytotoxins.

The provisional rejection of claims 1, 2, 7, 13-15, 17, 18, 20-23, 28, 34-36 and 38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 09/851,422 is maintained for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '422 application anticipate the instant claims.

The provisional rejection of claims 1, 2, 4-10, 13-23, 25-31, 34-39 and 60 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of

copending Application No. 09/851,422 in view of Glazier (U.S. 2003/0138432) is maintained for reasons of record.

Glazier teaches the targeting specific proteases of PSA (paragraphs 1329, 1354-1356), PSMA (paragraphs 710, 1015, 1019), matrix metalloproteinases (paragraphs 0698, 699 and 727-732). Glazier teaches the targeting of tumor neovasculature for drug delivery (paragraphs 958, 1291) and the use of the "RGD" targeting sequence (paragraphs 954-955). It would have been prima facie obvious at the time the invention was made to direct the procytotoxin of the invention to a tumor cell or the neovasculature surrounding a tumor cell to allow for more specificity of treatment. One of skill in the art would have been motivated to do so by the teachings of Glazier.

The provisional rejection of claims 1, 2, 7, 13-15, 17, 18, 20-23, 28, 34-36 and 38 are under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of copending Application No. 11/131,443 is maintained for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '443 application anticipate the instant claims.

The objection to claims 54-57 for being dependent upon a rejected base claim is maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
7/9/2006